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FOR: AMIDE COMPOUNDS

REQUEST FOR PRIORITY UNDER 35 U.S.C. 119
AND THE INTERNATIONAL CONVENTION

Assistant Commissioner for Patents
Washington, D.C. 20231

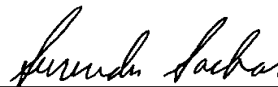
Sir:

In the matter of the above-identified application for patent, notice is hereby given that the applicant claims as priority:

<u>COUNTRY</u>	<u>APPLICATION NO</u>	<u>DAY/MONTH/YEAR</u>
Australia	PQ3198	01 October 1999

Certified copies of the corresponding Convention application(s) were submitted to the International Bureau in PCT Application No. PCT/JP00/06623. Receipt of the certified copy(s) by the International Bureau in a timely manner under PCT Rule 17.1(a) has been acknowledged as evidenced by the attached PCT/IB/304.

Respectfully submitted,
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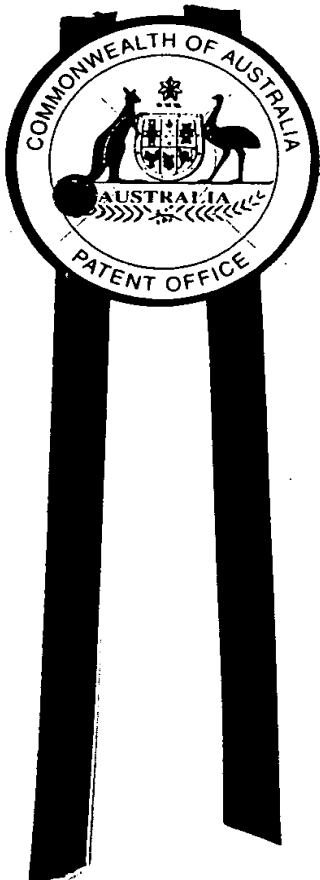
I, KAY WARD, ACTING MANAGER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. PQ 3198 for a patent by FUJISAWA PHARMACEUTICAL CO., LTD. filed on 01 October 1999.

WITNESS my hand this
Twelfth day of September 2000

K Ward

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PROVISIONAL SPECIFICATION
for the invention entitled:

"Amide Compounds"

The invention is described in the following statement:

DESCRIPTION

AMIDE COMPOUNDS

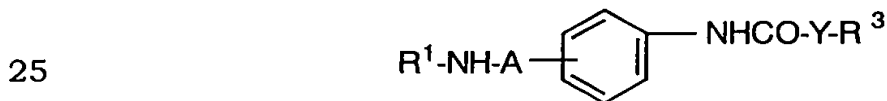
5 TECHNICAL FIELD

The present invention relates to novel amide compounds and salts thereof. More particularly, it relates to novel amide compounds and salts thereof which have pharmacological activities such as 5-hydroxytryptamine (5-HT) antagonism and the like.

10 Said amide compounds and their salts are useful as a 5-HT antagonist for treating or preventing central nervous system (CNS) disorders such as anxiety, depression, obsessive compulsive disorders, migraine, anorexia, Alzheimer's disease, sleep disorders, bulimia, panic attacks, withdrawal from drug abuse (e.g., with cocaine, ethanol,
15 nicotine and benzodiazepines), schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus in human being and animals.

BACKGROUND ART

20 With regard to the state of the art in this field, for example, the following amide compounds are disclosed in Japanese Patent Kokai No. Hei 11(1999)-130750.



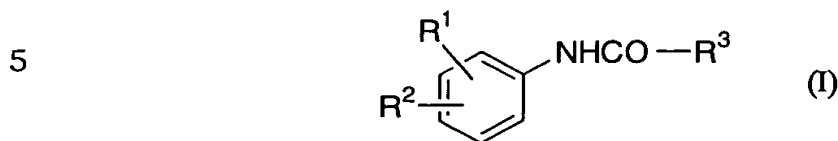
wherein, R¹ is quinolyl, quinazolinyl, isoquinolyl or pyridyl group, R³ is phenyl, cyclo(lower)alkyl, indolyl, lower alkylindazolyl or 2,3-dihydroindolyl group, Y is a single bond, lower alkylene or lower
30 alkenylene group, and A is lower alkylene group.

DISCLOSURE OF INVENTION

As a result of an extensive study, the inventors of the present invention found some amide compounds which have strong

pharmacological activities.

The amide compounds of the present invention are novel and can be represented by the formula (I):



wherein

R¹ is selected from an imidazolyl, triazolyl, pyridyl, pyridazinyl, pyrimidinyl and pyrazinyl group, each of which may be substituted with one or more lower alkyl groups,

R² is a hydrogen atom or a lower alkyl group, and

R³ is a phenyl group substituted with thienyl or halophenyl; a thienyl group substituted with thienyl, phenyl or halophenyl; a pyrrolyl group substituted with phenyl; a thiazolyl group substituted with phenyl; an indolyl group substituted with lower alkyl and/or halo(lower)alkyl; a fluorenyl group; or a carbazolyl group, provided that

(1) the imidazolyl group for R¹ is substituted with one or more alkyl groups, when R³ is a phenyl group substituted thienyl; an indolyl group substituted with lower alkyl; or carbazolyl group,

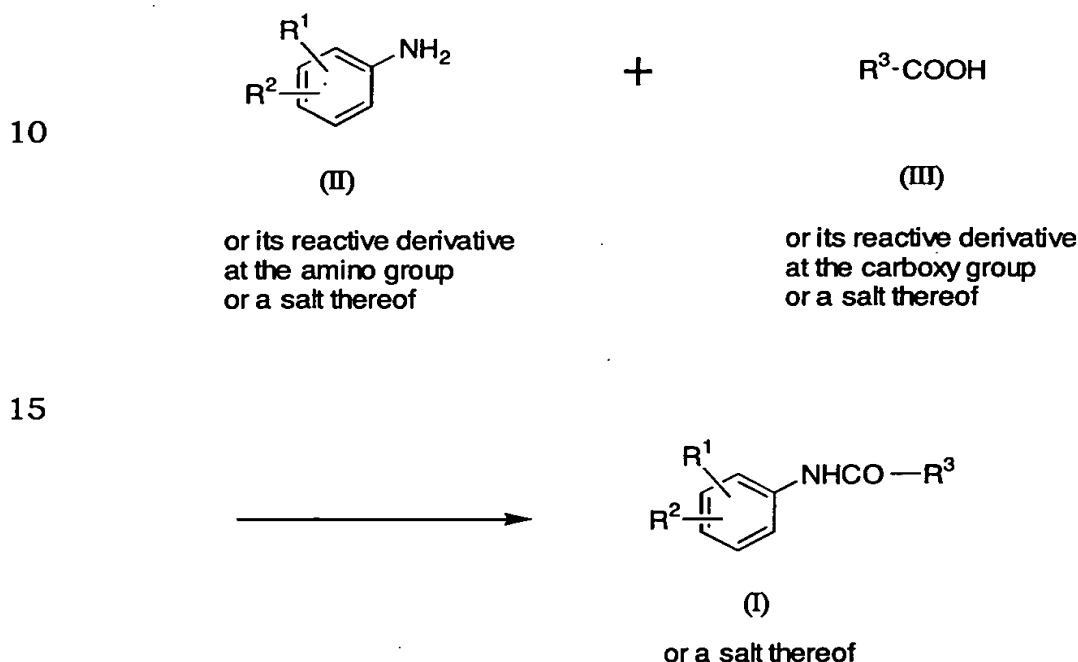
(2) the imidazolyl group for R¹ is substituted with two lower alkyl groups, when R³ is a phenyl group substituted with halophenyl, or

(3) R¹ is pyridyl group, pyridazinyl group, pyrimidinyl group or pyrazinyl group, when R³ is fluorenyl group.

Suitable salts of the compounds (I) are conventional non-toxic pharmaceutically acceptable salts and may include salts with inorganic bases, for example, alkali metals (e.g. sodium or potassium), alkaline earth metals (e.g. calcium or magnesium), ammonium; salts with organic bases, for example, organic amines (e.g. triethylamine, pyridine, picoline, ethanolamine, triethanolamine, dicyclohexylamine, or N,N'-dibenzylethylenediamine); inorganic acid addition salts (e.g. hydrochloride, hydrobromide, hydriodide, sulfate or phosphate); organic carboxylic or sulfonic acid addition salts (e.g. formate, acetate,

trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate or p-toluenesulfonate); salts with basic or acidic amino acids (e.g. arginine, aspartate or glutamate); and the like, and preferable example thereof is the acid addition salts.

5 According to the present invention, the object compounds (I) can be prepared by the following process:



wherein R¹, R² and R³ are each as defined above.

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention include within the scope are explained in detail in the following.

The term "lower" is intended to mean 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms, unless otherwise indicated.

Suitable lower alkyl groups and lower alkyl moieties in the halo(lower)alkyl groups may include straight or branched ones, having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl and hexyl, and preferably the ones having 1 to 4 carbon atom(s), among which the most preferred one is methyl.

Suitable halo(lower)alkyl groups may include lower alkyl groups

substituted with one or more halogen atoms such as fluoromethyl, fluoroethyl, fluoropropyl, trifluoromethyl, chloromethyl, dichloromethyl, chloroethyl, chloropropyl, bromomethyl, bromoethyl, bromopropyl, iodomethyl, iodoethyl, iodopropyl, and the like.

5 Suitable halophenyl groups may include fluorophenyl, difluorophenyl, chlorophenyl, dichlorophenyl, trichlorophenyl, bromophenyl, dibromophenyl, tribromophenyl, iodophenyl, and the like.

 When imidazolyl, triazolyl, pyridyl, pyridazinyl, pyrimidinyl or pyrazinyl groups for R¹ is substituted with two or more lower alkyl
10 groups, said lower alkyl groups may be the same or different from each other.

 And also, when indolyl group for R³ is substituted with two or more lower alkyl groups and/or two or more halo(lower)alkyl groups, said lower alkyl groups and halo(lower)alkyl groups may be the same or
15 different each to other.

 The process for preparing the object compounds (I) is explained in detail in the following.

 The object compound (I) and its salt can be prepared by reacting a compound (II) or its reactive derivative at the amino group or a salt
20 thereof with a compound (III) or its reactive derivative at the carboxy group or a salt thereof.

 Suitable reactive derivatives at the amino group of the compound (II) may include Schiff's base type imine or its tautomeric enamine type isomer formed by the reaction of the compound (II) with a
25 carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (II) with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide, bis(trimethylsilyl)urea or the like; a
30 derivative formed by the reaction of a compound (II) with phosphorus trichloride or phosgene, and the like.

 Suitable salts of the compound (II) and its reactive derivative can be referred to those as exemplified for the compound(I).

 Suitable reactive derivatives at the carboxy group of the compound (III) may include the acid halides, acid anhydrides, activated

amides, activated esters, and the like.

Suitable examples of such reactive derivatives may be the acid chloride; the acid azide; the mixed acid anhydride with an acid such as substituted phosphoric acid [e.g. dialkylphosphoric acid, 5 phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid or halogenated phosphoric acid], dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid [e.g. methanesulfonic acid], aliphatic carboxylic acid [e.g. acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, 10 isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid] or aromatic carboxylic acid [e.g. benzoic acid]; symmetrical acid anhydride; activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; or activated ester [e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl $[(CH_3)_2N^+=CH-]$ ester, vinyl 15 ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester or 8-quinolyl thioester], or ester with an N-hydroxy 20 compound [e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide or 1-hydroxy-1H-benzotriazole], and the like.

The reactive derivative can optionally be selected from the above according to the kind of the compound (III) to be used.

25 Suitable salts of the compound (III) and its reactive derivative may be the base salts such as alkali metal salts [e.g. sodium salt or potassium salt], alkaline earth metal salts [e.g. calcium salt or magnesium salt], ammonium salts, organic base salts [e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, 30 dicyclohexylamine salt or N,N'-dibenzylethylenediamine salt], or the like, and acid addition salts as exemplified for the compound (I).

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g. methanol or ethanol], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride,

tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction, or a mixture thereof.

In this reaction, when the compound (III) is used in a free acid
5 form or its salt form, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)
10 carbodiimide; N,N'-carbonylbis-(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus
15 oxychloride (phosphoryl chloride); phosphorus trichloride; diphenyl phosphorylazide; thionyl chloride; oxalyl chloride; lower alkyl haloformate [e.g. ethyl chloroformate, isopropyl chloroformate, etc.]; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)-isoxazolium hydroxide intramolecular salt;
20 benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorus oxychloride or the like.

25 The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower) alkylmorpholine, N,N-di(lower)alkylbenzylamine, or the like,

The reaction is usually carried out under cooling to warming,
30 although the reaction temperature is not critical.

The object compound (I) of the present invention can be isolated and purified in a conventional manner, for example extraction, precipitation, fractional crystallization, recrystallization,

chromatography, and the like.

The object compound (I) thus obtained can be converted to its corresponding salt by the conventional method.

5 The object compound (I) and salts thereof may include solvates [e.g., enclosure compound (e.g., hydrate, etc.)].

Among the starting compounds (II) and (III), novel compounds can be prepared by the method described in the following Examples or similar method thereto.

10 In order to exhibit the usefulness of the present invention, the activities of the compounds (I) are shown in the following.

Test method:

15 ^[3H]-mesulergine binding

The affinity of the test drugs for the 5-HT_{2c} binding site can be determined by assessing their ability to displace ^[3H]-mesulergine in the rat prefrontal cortex. The method employed was similar to that of Pazos et al, 1984.

20 The membrane suspension (500 µl) was incubated with ^[3H]-mesulergine (1 nM) in Tris HCl buffer containing CaCl₂ 4 mM and ascorbic acid 0.1 % (pH 7.4) at 37 °C for 30 minutes. Non-specific binding was measured in the presence of mianserin (1 µM). 30 nM spiperone was used to prevent binding to 5-HT_{2A} sites. Test drugs (10⁻⁶
25 M) were added in a volume of 100 µl. The total assay volume was 1000 µl. Incubation was stopped by rapid filtration using a Brandel cell harvester and radioactivity measured by scintillation counting.

The IC₅₀ values were determined using a four parameter logistic program (DeLean 1978) and the pK_i (the negative logarithm of the
30 inhibition constant) calculated from the Cheng Prusoff equation where:

$$K_i = \frac{IC_{50}}{1+C/K_d}$$

K_i = inhibition constant

c = concentration of ^[3H]-mesulergine

K_d = affinity of mesulergine for 5-HT_{2c}

binding site.

Test Compounds:

- 5 (1) N-(1-Methyl-1H-indol-5-yl)-N'-(3-pyridyl)urea
(reference compound)
(2) N-(3-(pyridin-2-yl)phenyl)fluorene-1-carboxamide (Example 1)
(3) N-(3-(pyrimidin-2-yl)phenyl)fluorene-1-carboxamide (Example 2)
(4) 9H-fluorene-1-carboxylic acid (3-pyridazin-3-yl-phenyl)-amide
10 (Example 4)
(5) 9H-fluorene-1-carboxylic acid (3-pyridazin-4-yl-phenyl)-amide
(Example 6)

Test result:

Compound	Inhibition (%)
(1)	21
(2)	74
(3)	92
(4)	31
(5)	64

15

As shown in above, the object compounds (I) of the present invention exhibit pharmacological activities such as 5-HT antagonism, especially, 5-HT_{2c} antagonism, and therefore are useful as 5-HT antagonist for treating or preventing central nervous system (CNS) disorders such as anxiety, depression, obsessive compulsive disorders, migraine, anorexia, Alzheimer's disease, sleep disorders, bulimia, panic attacks, withdrawal from drug abuse (e.g., with cocaine, ethanol, nicotine and benzodiazepines), schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus, and the like.

20

25

For therapeutic or preventive administration, the object compounds (I) of the present invention are used in a form of conventional

pharmaceutical preparation which contains said compound as an active ingredient, in admixture with pharmaceutically acceptable carriers such as an organic or inorganic solid or liquid excipient which is suitable for oral, parenteral and external administration. The pharmaceutical
5 preparations may be in a solid form such as tablet, granule, powder or capsule, or in a liquid form such as solution, suspension, syrup, emulsion or lemonade.

If needed, there may be included in the above preparations auxiliary substances, stabilizing agents, wetting agents and other
10 commonly used additives such as lactose, citric acid, tartaric acid, stearic acid, magnesium stearate, terra alba, sucrose, corn starch, talc, gelatin, agar, pectin, peanut oil, olive oil, cacao butter, ethylene glycol, and the like.

While the dosage of the compound (I) may vary from and also
15 depend upon the age, conditions of the patient, kind of diseases or conditions, kind of the compound (I) to be applied, etc., in general, 0.01-500 mg of a compound (I) may be administered to a patient per day.

An average single dose of about 0.05 mg, 0.1 mg, 0.25 mg, 0.5 mg, 1 mg, 20 mg, 50 mg, 100 mg of a compound (I) may be used in
20 treating the diseases.

The following Examples are given for illustrating the present invention, but it is to be noted that the scope of the present invention is not limited by these Examples.

25

(to be continued on the next page)

BEST MODE FOR CARRYING OUT THE INVENTION

The following Examples are given only for the purpose of illustrating the present invention in more detail.

5 Example 1

To a suspension of 3-(pyridin-3-yl)aniline (0.17 g) and pyridine (0.24 ml) in dichloromethane (3 ml) was dropwise added a solution of the fluorene-1-carbonyl chloride (0.23g) in dichloromethane (2 ml) followed by stirring for 2 hours. The mixture was diluted with dichloromethane and washed with an aqueous solution of sodium hydrogen carbonate and brine. The separated organic layer was dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by a column chromatography (silica gel 25g, 2% methanol in dichloromethane) to give N-[3-(pyridin-2-yl)phenyl]fluorene-1-carboxamide (0.317 g, 87.6 %).

NMR (DMSO- d_6 , δ): 4.23 (2H, s), 7.3 - 7.7 (7H, m), 7.78 (1H, d, $J = 7.7$ Hz), 7.8 - 8.1 (4H, m), 8.18 (1H, s), 8.60 (1H, d, $J = 4.8$ Hz), 8.88 (1H, s), 10.47 (1H, s)

APCI- Mass m/z : 363 ($M^+ + 1$).

20

Example 2

To a suspension of 3-(pyrimidin-5-yl)aniline (0.17g) and pyridine (0.24ml) in dichloromethane (3ml) was dropwise added a solution of the fluorene-1-carbonyl chloride (0.23g) in dichloromethane (5 ml) followed by stirring for 2 hours. The mixture was diluted with dichloromethane and washed with an aqueous solution of sodium hydrogen carbonate and brine. The separated organic layer was dried over sodium sulfate and evaporated. The residue was purified by a column chromatography (silica gel 25g, 2% methanol in dichloromethane) to give N-[3-(pyrimidin-2-yl)phenyl]fluorene-1-carboxamide (0.222 g, 61.2 %).

30

NMR (DMSO- d_6 , δ): 4.23 (2H, s), 7.3 - 7.5 (2H, m), 7.5-7.7 (4H, m), 7.78 (1H, d, $J = 8.0$ Hz), 7.8 - 8.1 (2H, m), 8.13 (1H, d, $J = 7.7$ Hz), 8.21 (1H, s), 9.12 (2H, s), 9.23 (1H, s), 10.51 (1H, s)

APCI- Mass m/z : 364 ($M^+ + 1$).

Example 3

To a suspension of 9H-carbazole-1-carboxylic acid (106 mg) and 1-hydroxybenzotriazole (81 mg) in dichloromethane (2 ml) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (144 mg) and the mixture was stirred for 15 minutes. After adding 3-(1,2-dimethylimidazol-5-yl)aniline (94 mg) and 4-dimethylaminopyridine (92 mg), the mixture was stirred for 60 hours. The residue was evaporated under reduced pressure and purified by a column chromatography (silica gel 25g, 2% methanol in dichloromethane) to give 9H-carbazole-1-carboxylic acid [3-(2,3-dimethyl-3H-imidazol-4-yl)-phenyl]-amide (101 mg, 53.2 %).

NMR (DMSO- d_6 , δ): 2.37 (3H, s), 3.59 (3H, s), 6.90 (1H, s), 7.2-7.6 (5H, m), 7.71 (1H, d, $J = 8.0$ Hz), 7.89 (1H, d, $J = 8.2$ Hz), 7.96 (1H, s), 8.11 (1H, d, $J = 7.4$ Hz), 8.18 (1H, d, $J = 7.7$ Hz), 8.38 (1H, d, $J = 7.7$ Hz), 10.47 (1H, s), 11.49 (1H, s)

APCI- Mass m/z : 381 ($M^+ + 1$).

Preparation 4(1)

To a suspension of 3,6-dichloropyridazine (2.98 g) and 3-nitrophenylboronic acid (1.67 g) and tetrakis(triphenylphosphine)palladium (578 mg) in 1,2-dimethoxyethane (30 ml) was added an aqueous solution of sodium carbonate (2M, 15 ml), and the mixture was stirred at 80 °C for 3 hours. The mixture was diluted with ethyl acetate, and then washed with water and brine. The organic layer was dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by a column chromatography (silica gel 50 g, 30 % ethyl acetate in n-hexane) to give 3-chloro-6-(3-nitro-phenyl)-pyridazine (0.246g, 10.4 %).

NMR (DMSO- d_6 , δ): 7.88 (1H, t, $J = 8.1$ Hz), 8.13 (1H, d, $J = 9.0$ Hz), 8.41 (1H, dt, $J = 6.8$ Hz, 1.2Hz), 8.54 (1H, d, $J = 9.0$ Hz), 8.6-8.8 (1H, m), 8.97 (1H, t, $J = 1.2$ Hz)

APCI- Mass m/z : 236 ($M^+ + 1$).

Preparation 4(2)

A suspension of 3-chloro-6-(3-nitro-phenyl)pyridazine (0.34 g) in tetrahydrofuran (5 ml) and ethanol (5 ml) was hydrogenated over palladium on carbon (10 % w/w, 50 % wet, 100 mg) under hydrogen for 10 hours. The catalyst was filtered off and the filtrate was evaporated. The residue was diluted with ethyl acetate and an aqueous solution of sodium hydrogen carbonate. The separated organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give 3-pyridazin-3-yl-phenylamine (155 mg, 62.8 %).

5 10 NMR (DMSO- d_6 , δ): 5.29 (2H, broad s), 6.72 (1H, t, $J = 2.8\text{Hz}$), 7.1-8.0 (4H, m), 8.04 (1H, d, $J = 8.6\text{Hz}$), 9.16 (1H, dd, $J = 5.0\text{Hz}$, 1.6Hz)

APCI- Mass m/z : 172 ($M^+ + 1$).

Example 4

15 To a suspension of 1-fluorencarboxylic acid (184 mg) and oxalyl chloride (0.2 ml) in dichloromethane (4 ml) was added N,N-dimethylformamide (0.01 ml) and the mixture was stirred for 2 hours. The resultant solution was evaporated to give a crude acid chloride. To a suspension of 3-pyridazin-3-yl-phenylamine (150 mg) and pyridine (0.21

20 ml) in dichloromethane (2 ml) was dropwise added a solution of the acid chloride obtained above in dichloromethane (5 ml) followed by stirring for an hour. The mixture was diluted with dichloromethane and washed with an aqueous solution of sodium hydrogen carbonate and brine. The separated organic layer was dried over sodium sulfate and evaporated

25 under reduced pressure. The residue was purified by a column chromatography (silica gel 25g, 2% methanol in dichloromethane) to give 9H-fluorene-1-carboxylic acid (3-pyridazin-3-yl-phenyl)-amide (44 mg, 13.8 %).

30 NMR (DMSO- d_6 , δ): 4.24 (2H, s), 7.3-7.5 (2H, m), 7.5-7.7 (3H, m), 7-7-7.9 (3H, m), 7.99 (1H, dd, $J = 7.0\text{Hz}$, 1.8Hz), 8.1-8.3 (2H, m), 8.70 (1H, t, $J = 3.6\text{Hz}$), 9.24 (1H, dd, $J = 4.9\text{Hz}$, 1.5Hz), 10.54 (1H, s)

APCI- Mass m/z : 364 ($M^+ + 1$).

Preparation 5(1)

To a suspension of 2-chloropyrazine (1.14 g) and 3-nitrophenylboronic acid (2.00 g) and tetrakis(triphenylphosphine)palladium (346 mg) in 1,2-dimethoxyethane (30 ml) was added an aqueous solution of sodium carbonate (2M, 12 ml) followed by stirring at 80 °C for 18 hours. The mixture was diluted with dichloromethane and washed with water and brine. The organic layer was dried over magnesium sulfate and evaporated under reduced pressure. The residue was triturated with methanol and collected by filtration. The obtained product was washed with methanol and diisopropyl ether and dried to give 2-(3-nitrophenyl)pyrazine (1.78g, 88.6 %).

NMR (CDCl₃, δ): 7.26 (1H, s), 7.67 (1H, t, J = 8.0Hz), 8.36 (1H, dt, J = 7.7 Hz, 1.5 Hz), 8.63 (1H, d, J = 2.4Hz), 8.70 (1H, t, J = 4.0Hz), 8.93 (1H, t, J = 4.0Hz), 9.13 (1H, t, J = 1.5Hz)

APCI- Mass m/z : 202 (M⁺+1).

Preparation 5(2)

A suspension of 2-(3-nitrophenyl)pyrazine (500 mg) in tetrahydrofuran (5ml) and ethanol (5 ml) was hydrogenated over palladium on carbon (10 % w/w, 50 % wet, 200 mg) under hydrogen for 6 hours. The catalyst was filtered off and the filtrate was evaporated. The residue was crystallized from dichloromethane-diisopropyl ether to give 2-(3-aminophenyl)pyrazine(410 mg, 96.5 %).

NMR (CDCl₃, δ): 3.82(2H, s), 6.81 (1H, dt, J = 6.0Hz, 1.2Hz), 7.3-7.6 (3H, m), 8.49 (1H, d, J = 2.5Hz), 8.60 (1H, t, J = 1.3Hz), 9.00 (1H, d, J = 1.5Hz)

APCI- Mass m/z : 171 (M⁺+1).

Example 5

To a suspension of 3-(pyrazin-2-yl)aniline (0.12g) and pyridine (0.17ml) in dichloromethane (3ml) was dropwise added a solution of the fluorene-1-carbonyl chloride (0.16g) in dichloromethane (3 ml) followed by stirring for 2 hours. The mixture was diluted with dichloromethane and washed with an aqueous solution of sodium hydrogen carbonate and brine. The separated organic layer was dried over sodium sulfate and

evaporated under reduced pressure. The residue was purified by a column chromatography (silica gel 25g, 2% methanol in dichloromethane) to give N-[3-(pyrazin-2-yl)phenyl]fluorene-1-carboxamide (0.193 g, 76.0 %).

- 5 NMR (DMSO- d_6 , δ): 4.24 (2H, s), 7.3 - 7.7 (5H, m), 7.79 (1H, d, J = 7.6Hz), 7.8 - 8.1 (3H, m), 8.13 (1H, d, J = 6.8Hz), 8.6-8.7 (2H, m), 8.76 (1H, t, J = 1.2Hz), 9.23 (1H, d, J = 1.5Hz), 10.52 (1H, s)
APCI- Mass m/z : 364 (M^{++1}).

10 Preparation 6(1)

- A suspension of 3-nitrobenzyl cyanide (1.62 g), glyoxylic acid monohydrate (1.38 g) and potassium carbonate (3.59 g) in methanol (20 ml) was stirred for 5 hours. The precipitate was collected by filtration, washed with dichloromethane and dried. The precipitate was suspended
15 in water and stirred for an hour. The insoluble material was collected by filtration and dried to give 3-cyano-3-(3-nitro-phenyl)-acrylic acid potassium salt (2.18 g, 85.2 %).

ESI-Mass m/z : 217 ($M-K^+$)

- NMR (DMSO- d_6 , δ): 7.36 (1H, s), 7.73 (1H, t, J = 8.0Hz), 8.10 (1H, d, J =
20 7.9Hz), 8.24 (1H, d, J = 7.9HZ), 8.62 (1H, s)

Preparation 6(2)

- To a suspension of 3-cyano-3-(3-nitro-phenyl)-acrylic acid potassium salt (1.28 g) in formic acid (10 ml) and water (1 ml) was added
25 sulfuric acid (1ml), and the mixture was refluxed for 3 hours. After cooling, the mixture was poured into water. The resulting precipitate was collected by filtration and dried to give 3-(3-nitro-phenyl)-furan-2,5-dione(0.69 g).

- NMR ($CDCl_3$, δ): 7.24 (1H, d, J = 8.9Hz), 7.76 (1H, d, J = 8.1Hz), 8.3-8.5
30 (2H, m), 8.81 (1H, s)

APCI- Mass m/z : 220 (M^{++1}).

Preparation 6(3)

To a suspension of 3-(3-nitro-phenyl)-furan-2,5-dione (673 mg) in

acetic acid (7 ml) was added hydrazine hydrate (0.18 ml), and the mixture was refluxed for 5 hours. The mixture was poured into water. The resulting precipitate was collected by filtration and dried to give 4-(3-nitro-phenyl)-1,2-dihydro-pyridazine-3,6-dione (0.68 g, 95.0%).

- 5 NMR (DMSO- d_6 , δ): 7.43 (1H, s), 7.6-8.4 (3H, m), 8.81 (1H, s), 11.04 (1H, broad s), 12.31 (1H, broad s)
APCI- Mass m/z : 234 ($M^+ + 1$).

Preparation 6(4)

- 10 A suspension of 4-(3-nitro-phenyl)-1,2-dihydro-pyridazine-3,6-dione (668 mg) in phosphorus oxychloride (6 ml) was refluxed for 2 hours. The mixture was concentrated under reduced pressure and diluted with ethyl acetate. The solution was washed with an aqueous solution of sodium hydrogen carbonate and brine and dried over magnesium sulfate.
- 15 The organic layer was evaporated under reduced pressure. The residue was purified by a column chromatography (silica gel 25 g, dichloromethane) to give 3,6-dichloro-4-(3-nitro-phenyl)pyridazine (385 mg, 49.9 %).
- 20 NMR ($CDCl_3$, δ): 7.26(1H, s), 7.57 (1H, s), 7.76 (1H, t, $J = 8.1$ Hz), 7.86 (1H, d, $J = 7.9$ Hz), 8.4-8.6 (2H, m)
APCI- Mass m/z : 270 ($M^+ + 1$).

Preparation 6(5)

- 25 A suspension of 3,6-dichloro-4-(3-nitro-phenyl)pyridazine (0.19 g) and sodium hydrogen carbonate (147 mg) in tetrahydrofuran (2 ml) and ethanol (5 ml) was hydrogenated over palladium on carbon (10 % w/w, 50 % wet, 100 mg) under hydrogen for 3 hours. The catalyst was filtered off, and the filtrate was evaporated. The residue was diluted with ethyl acetate and an aqueous solution of sodium hydrogen carbonate. The
- 30 separated organic layer was washed with brine and dried over potassium carbonate. The organic layer was evaporated under reduced pressure to give 3-pyridazin-4-yl-phenylamine (106 mg, 88.3 %).
- NMR (DMSO- d_6 , δ): 5.35 (2H, broad s), 6.72 (1H, t, $J = 7.6$ Hz), 7.0-7.2 (2H, m), 7.20 (1H, t, $J = 8.0$ Hz), 7.85 (1H, dd, $J = 5.6$ Hz, 2.4Hz), 9.23 (H, d, $J =$

5.6Hz), 9.49 (1H, s)

APCI- Mass m/z : 172 (M^{++1}).

Example 6

- 5 To a suspension of 1-fluorene-1-carboxylic acid (120 mg) and oxalyl chloride (0.12 ml) in dichloromethane (2.5 ml) was added N,N-dimethylformamide (0.01 ml) and the mixture was stirred for 2 hours. The resultant solution was evaporated to give a crude acid chloride. To a suspension of 3-pyridazin-4-yl-phenylamine (98 mg) and pyridine (0.14
- 10 ml) in dichloromethane (2 ml) was dropwise added a solution of the acid chloride obtained above in dichloromethane (5 ml), and the mixture was stirred for an hour. The mixture was diluted with dichloromethane and washed with an aqueous solution of sodium hydrogen carbonate and brine. The separated organic layer was dried over sodium sulfate and
- 15 evaporated under reduced pressure. The residue was purified by a column chromatography (silica gel 25g, 2% methanol in dichloromethane) to give 9H-fluorene-1-carboxylic acid (3-pyridazin-4-yl-phenyl)-amide (133 mg, 63.9 %).
- 20 NMR (DMSO- d_6 , δ): 4.23 (2H, s), 7.3-7.7 (6H, m), 7.79 (1H, d, $J = 7.0$ Hz), 7.9-8.1 (3H, m), 8.14 (1H, d, $J = 6.9$ Hz), 8.34 (1H, s), 9.32 (1H, d, $J = 5.5$ Hz), 9.60 (1H, s), 10.56 (1H, s)
- APCI- Mass m/z : 364 (M^{++1}).

Preparation 7

- 25 To a solution of 2-(3-methoxycarbonylphenyl)thiophene (1.29 g) in methanol (15 ml) and tetrahydrofuran (5 ml) was added an aqueous solution of sodium hydroxide (1N, 8.87 ml) followed by stirring for 2 hours at 60°C. To the mixture was added hydrochloric acid (1N, 10 ml). The resulting precipitate was collected by filtration and dried to give 2-(3-
- 30 carboxyphenyl)thiophene (1.13g, 93.4 %).
- NMR (DMSO- d_6 , δ): 7.17 (1H, t, $J = 4.4$ Hz), 7.5-7.7 (3H, m), 7.87 (1H, d, $J = 7.8$ Hz), 7.93 (1H, d, $J = 7.8$ Hz), 8.15 (1H, s), 13.19 (1H, broad s)
- ESI- Mass m/z : 203 (M^{+-1}).

Example 7

To a suspension of 3-(thiophen-2-yl)benzoic acid (102 mg) and oxalyl chloride (0.2 ml) in dichloromethane (2 ml) was added N,N-dimethylformamide (0.01 ml) and the mixture was stirred for an hour.

- 5 The resultant solution was evaporated to give a crude acid chloride. To a suspension of 3-(1,2-dimethylimidazol-5-yl)aniline (94 mg) and pyridine (0.12 ml) in dichloromethane (2 ml) was dropwise added a solution of the acid chloride obtained above in dichloromethane (2 ml), and the mixture was stirred for 12 hours. The mixture was diluted with dichloromethane and washed with an aqueous solution of sodium hydrogen carbonate and
10 brine. The separated organic layer was dried over sodium sulfate and evaporated. The residue was purified with column chromatography (silica gel 25g, 3% methanol in dichloromethane) to give N-[3-(2,3-dimethyl-3H-imidazol-4-yl)-phenyl]-3-thiophen-2-yl-benzamide (140 mg,
15 74.9 %).

NMR (DMSO- d_6 , δ): 2.36 (3H, s), 3.59 (3H, s), 6.89 (1H, s), 7.1-7.3 (2H, m), 7.44 (1H, t, $J = 7.9\text{Hz}$), 7.6-7.8 (3H, m), 7.79 (1H, d, $J = 8.0\text{Hz}$), 7.8-8.0 (3H, m), 8.19 (1H, s), 10.45 (1H, s)

APCI- Mass m/z : 374 ($M^+ + 1$).

20

Example 8

To a suspension of 9H-carbazole-1-carboxylic acid (422 mg) and 1-hydroxybenzotriazole (324 mg) in dichloromethane (10 ml) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (575 mg)
25 and the mixture was stirred for 15 minutes. After adding 3-(pyrimidin-5-yl)aniline (360 mg) and 4-dimethylaminopyridine (367 mg), the mixture was stirred for 48 hours. The residue was evaporated under reduced pressure and purified by a column chromatography (silica gel 25g, 2% methanol in dichloromethane) to give 9H-carbazole-1-carboxylic acid [3-(pyrimidin-5-yl)-phenyl]-amide (314 mg, 43.1 %).
30

NMR (DMSO- d_6 , δ): 7.20 (1H, t, $J = 7.4\text{Hz}$), 7.33 (1H, t, $J = 7.7\text{Hz}$), 7.42 (1H, t, $J = 7.6\text{Hz}$), 7.58 (2H, d, $J = 5.1\text{Hz}$), 7.72 (1H, d, $J = 8.0\text{Hz}$), 7.9-8.1 (1H, m), 8.17 (2H, dd, $J = 7.4\text{Hz}$, 4.0Hz), 8.35 (1H, s), 8.39 (1H, d, $J = 7.5\text{Hz}$), 9.15 (2H, s), 9.23 (1H, s), 10.56 (1H, s), 11.54 (1H, s)

APCI- Mass m/z : 365 ($M^{+}+1$).

Example 9

To a suspension of 9H-carbazole-1-carboxylic acid (148 mg) and
5 1-hydroxybenzotriazole (114 mg) in dichloromethane (3 ml) was added
1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (201 mg)
and the mixture was stirred for 15 minutes. After adding 3-(1,2,4-
triazol-1-yl)aniline (123 mg) and 4-dimethylaminopyridine (128 mg), the
mixture was stirred for 24 hours. The mixture was evaporated and
10 purified by a column chromatography (silica gel 25g, 2% methanol in
dichloromethane) to give 9H-carbazole-1-carboxylic acid [3-(1,2,4-
triazol-1-yl)-phenyl]-amide (103 mg, 41.5 %).

NMR ($\text{DMSO}-d_6$, δ): 7.20(1H, t, $J = 7.3\text{Hz}$), 7.32 (1H, t, $J = 7.5\text{Hz}$), 7.42
(1H, t, $J = 7.3\text{Hz}$), 7.5-7.7 (2H, m), 7.73 (1H, d, $J = 8.2\text{ Hz}$), 7.86 (1H, d, J
15 $= 7.3\text{Hz}$), 8.1-8.3 (2H, m), 8.28 (1H, s), 8.40 (1H, d, $J = 7.5\text{ Hz}$), 8.61 (1H,
s), 9.30 (1H, s), 10.64 (1H, s), 11.57 (1H, s).

APCI- Mass m/z : 354 ($M^{+}+1$).

Preparation 10(1)

20 To a suspension of 2-bromo-5-methoxycarbonylthiophene (1.11
g) and phenylboronic acid (0.79 g) and
tetrakis(triphenylphosphine)palladium (289 mg) in 1,2-dimethoxyethane
(10 ml) was added an aqueous solution of sodium carbonate (2M, 6.5 ml)
followed by stirring at 80°C for 18 hours. The mixture was diluted with
25 dichloromethane and washed with water and brine. The mixture was
dried over magnesium sulfate and evaporated under reduced pressure.
The residue was triturated with methanol. The resulting precipitate was
collected by filtration, washed with methanol and diisopropyl ether and
dried to give 2-methoxycarbonyl-5-phenylthiophene (918 mg, 84.2 %).

30 NMR (CDCl_3 , δ): 3.84 (3H, s), 7.4-7.6 (3H, m), 7.62 (1H, d, $J = 4.0\text{Hz}$),
7.7-7.9 (2H, m), 7.81 (1H, d, $J = 4.0\text{Hz}$)

APCI- Mass m/z : 219 ($M^{+}+1$).

Preparation 10(2)

To a solution of 2-methoxycarbonyl-5-phenylthiophene (437 mg) in methanol (5 ml) and tetrahydrofuran (5 ml) was added an aqueous solution of sodium hydroxide (1N, 3 ml) followed by stirring for 2 hours. To the mixture was added hydrochloric acid (1N, 5 ml). The precipitate was collected by filtration and dried to give 5-phenylthiophene-2-carboxylic acid (397 mg, 97.1 %).

NMR (DMSO- d_6 , δ): 7.3-7.5 (3H, m), 7.58 (1H, d, $J = 3.9\text{Hz}$), 7.6-7.8 (3H, m), 13.15 (1H, broad s)

ESI- Mass m/z : 203 ($M^+ - 1$).

10

Example 10

To a suspension of 5-phenylthiophene-2-carboxylic acid (102 mg) and oxalyl chloride (0.2 ml) in dichloromethane (2 ml) was added *N,N*-dimethylformamide (0.01 ml) and the mixture was stirred for an hour.

15 The resultant solution was evaporated under reduced pressure to give a crude acid chloride. To a suspension of 3-(1,2-dimethylimidazol-5-yl)aniline (94 mg) and pyridine (0.12 ml) in dichloromethane (2 ml) was dropwise added a solution of the acid chloride obtained above in dichloromethane (2 ml) followed by stirring for 12 hours. The mixture was diluted with dichloromethane and washed with an aqueous solution of sodium hydrogen carbonate and brine. The separated organic layer was dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by a column chromatography (silica gel 25g, 3% methanol in dichloromethane) to give 5-phenyl-thiophene-2-carboxylic acid [3-(2,3-dimethyl-3H-imidazol-4-yl)-phenyl]-amide (155 mg, 82.9 %).

20
25
NMR (DMSO- d_6 , δ): 2.36 (3H, s), 3.57 (3H, s), 6.89 (1H, s), 7.17 (1H, d, $J = 7.8\text{Hz}$), 7.4-7.6 (4H, m), 7.64 (1H, d, $J = 4.0\text{Hz}$), 7.7-7.9 (4H, m), 8.04 (1H, d, $J = 4.0\text{Hz}$), 10.34 (1H, s)

APCI- Mass m/z : 374 ($M^+ + 1$).

30

Preparation 11(1)

To a suspension of 5-bromopyrimidine (1.59 g) and 4-methyl-3-nitrophenylboronic acid (2.35 g) and tetrakis(triphenylphosphine)palladium (578 mg) in 1,2-dimethoxyethane

(20 ml) was added an aqueous solution of sodium carbonate (2M, 13 ml) followed by stirring at 80°C for 24 hours. The mixture was diluted with dichloromethane and washed with water and brine. The organic layer was dried over magnesium sulfate and evaporated under reduced pressure. The residue was triturated with methanol. The resulting precipitated was collected by filtration, washed with methanol and diisopropyl ether and dried to give 5-(4-methyl-3-nitrophenyl)-pyrimidine (918 mg, 84.2 %).

5

NMR (CDCl₃, δ): 2.56 (3H, s), 7.68 (1H, d, J = 8.0Hz), 8.10 (1H, dd, J = 8.0Hz, 1.8Hz), 8.42 (1H, d, J = 1.8Hz), 9.23 (3H, s)

10

APCI- Mass m/z : 216 (M⁺+1).

Preparation 11(2)

A suspension of 5-(4-methyl-3-nitrophenyl)-pyrimidine (258 mg) in tetrahydrofuran (5ml) and methanol (5 ml) was hydrogenated over palladium on carbon (10 % w/w, 50 % wet, 130 mg) under hydrogen for 4 hours. The catalyst was filtered off and the filtrate was evaporated to give 5-(3-amino-4-methylphenyl)pyrimidine (410 mg, 96.5 %).

15

NMR (CDCl₃, δ): 2.11 (3H, s), 5.05 (2H, s), 6.87 (1H, dd, J = 7.6Hz, 1.8Hz), 6.96 (1H, d, J = 1.8Hz), 7.07 (1H, d, J = 7.6Hz), 8.98 (2H, s), 9.12 (1H, s)

20

APCI- Mass m/z : 186 (M⁺+1).

Example 11

To a suspension of 9H-carbazole-1-carboxylic acid (148 mg) and 1-hydroxybenzotriazole (114 mg) in dichloromethane (3 ml) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (201 mg), and the mixture was stirred for 15 minutes. After adding 4-methyl-3-(pyrimidin-5-yl)aniline (136 mg) and 4-dimethylaminopyridine (128 mg), the mixture was stirred for 24 hours. The mixture was evaporated under reduced pressure and the residue was purified by a column chromatography (silica gel 25g, 2% methanol in dichloromethane) to give 9H-carbazole-1-carboxylic acid [4-methyl-3-(pyrimidin-5-yl)-phenyl]-amide (89 mg, 33.6 %).

25

30

NMR (DMSO-d₆, δ): 2.40 (3H, s), 7.20 (1H, t, J = 7.4Hz), 7.32 (1H, t, J =

7.6Hz), 7.4-7.6 (2H, m), 7.6-7.8 (2H, m), 7.96 (1H, s), 8.17 (2H, d, J =7.7 Hz), 8.39 (1H, d, J =7.6Hz), 9.17 (2H, s), 9.19 (1H, s), 10.19 (1H, s), 11.46 (1H, s)

APCI- Mass m/z : 379 (M^{++1}).

5

Example 12

To a suspension of 2-trifluoromethyl-3-methylindole-7-carboxylic acid (122 mg) and 3-(1,2-dimethylimidazol-5-yl)aniline (94 mg) in dichloromethane (3 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (144 mg) and 4-dimethylaminopyridine (30 mg). The mixture was stirred at ambient temperature for 18 hours and diluted with dichloromethane. The solution was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by a column chromatography (silica gel 25g, 2% methanol in dichloromethane) to give 3-methyl-2-trifluoromethyl-1H-indole-7-carboxylic acid [3-(1,2-dimethyl-1H-imidazol-5-yl)-phenyl]-amide (130 mg, 63.1 %).

NMR (DMSO- d_6 , δ): 2.36 (3H, s), 2.44 (3H, s), 3.57 (3H, s), 6.88 (1H, s), 7.17 (1H, d, J = 8.0Hz), 7.31 (1H, d, J = 8.0Hz), 7.45 (1H, t, J =7.8 Hz), 7.82 (1H, d, J =8.0Hz), 7.9-8.1 (3H, m), 10.50 (1H, s), 11.48 (1H, s)
APCI- Mass m/z : 413 (M^{++1}).

Example 13

To a suspension of 2,3-dimethylindole-7-carboxylic acid (95 mg) and 3-(1,2-dimethylimidazol-5-yl)aniline (94 mg) in dichloromethane (3 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (144 mg) and 4-dimethylaminopyridine (30 mg). The mixture was stirred at ambient temperature for 18 hours and diluted with dichloromethane. The solution was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by a column chromatography (silica gel 25g, 3% methanol in dichloromethane) to give 2,3-dimethyl-1H-indole-7-carboxylic acid [3-(1,2-dimethyl-1H-imidazol-5-yl)-phenyl]-amide (73 mg,

40.8 %).

NMR (DMSO- d_6 , δ): 2.18 (3H, s), 2.37 (6H, s), 3.57 (3H, s), 6.88 (1H, s), 7.06 (1H, d, $J = 7.6$ Hz), 7.15 (1H, d, $J = 10.1$ Hz), 7.44 (1H, d, $J = 7.9$ Hz), 7.61 (1H, d, $J = 7.6$ Hz), 7.72 (1H, d, $J = 7.3$ Hz), 7.85 (1H, d, $J = 8.2$ Hz),

5 7.92 (1H, s), 10.30 (1H, s), 10.76 (1H, s)

APCI- Mass m/z : 359 ($M^+ + 1$).

Example 14

To a suspension of 2-trifluoromethyl-3-methylindole-7-
10 carboxylic acid (122 mg) and 3-(pyrimidin-5-yl)aniline (86 mg) in
dichloromethane (3 ml) were added 1-ethyl-3-(3-
dimethylaminopropyl)carbodiimide hydrochloride (144 mg) and 4-
dimethylaminopyridine (30 mg). The mixture was stirred at ambient
temperature for 18 hours and diluted with dichloromethane. The
15 solution was washed with water and brine, dried over magnesium sulfate
and evaporated under reduced pressure. The residue was purified by a
column chromatography (silica gel 25g, 2% methanol in
dichloromethane) to give 3-methyl-2-trifluoromethyl-1H-indole-7-
carboxylic acid [3-(pyrimidin-5-yl)-phenyl]-amide (106 mg, 53.5 %).
20 NMR (DMSO- d_6 , δ): 2.45 (3H, s), 7.31 (1H, t, $J = 7.7$ Hz), 7.4-7.6 (2H, m),
7.9-8.1 (3H, m), 8.26 (1H, s), 9.13 (2H, s), 9.23 (1H, s), 10.59 (1H, s),
11.49 (1H, s)
APCI- Mass m/z : 397 ($M^+ + 1$).

25 Example 15

To a suspension of 3-(4-fluorophenyl)benzoic acid (151 mg) and
3-(1,2-dimethylimidazol-5-yl)aniline (131 mg) in dichloromethane (5 ml)
were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
hydrochloride (201 mg) and 4-dimethylaminopyridine (43 mg). The
30 mixture was stirred at ambient temperature for 18 hours and diluted with
dichloromethane. The solution was washed with water and brine, dried
over magnesium sulfate and evaporated under reduced pressure. The
residue was purified by a column chromatography (silica gel 25g, 3%
methanol in dichloromethane) to give 4'-fluoro-biphenyl-3-carboxylic acid

[3-(2,3-dimethyl-3H-imidazol-4-yl)-phenyl]-amide (240 mg, 88.9 %).

NMR (DMSO- d_6 , δ): 2.36(3H, s), 3.57 (3H, s), 6.88 (1H, s), 7.17 (1H, d, J = 7.7 Hz), 7.35 (2H, t, J = 8.9Hz), 7.45 (1H, t, J = 7.9Hz), 7.63 (1H, t, J = 7.7Hz), 7.8-8.1 (6H, m), 8.21 (1H, s), 10.43 (1H, s)

5 ESI- Mass m/z : 386 ($M^+ + 1$).

Preparation 16(1)

To a suspension of 2-bromo-5-methoxycarbonylthiophene (1.11 g), 4-fluorophenylboronic acid (0.91 g) and
10 tetrakis(triphenylphosphine)palladium (289 mg) in 1,2-dimethoxyethane (10 ml) was added aqueous solution of sodium carbonate (2M, 6.5 ml) followed by stirring at 80°C for 6 hours. The mixture was diluted with dichloromethane and washed with water and brine. The organic layer was dried over magnesium sulfate and evaporated under reduced
15 pressure. The residue was purified by a column chromatography (silica gel 50g, 30% dichloromethane in n-hexane) to give 2-methoxycarbonyl-5-(4-fluorophenyl)thiophene (1.16 g, 98.3 %).

NMR (CDCl₃, δ): 3.86 (3H, s), 7.32 (2H, t, J = 8.8Hz), 7.59 (1H, d, J = 4.0Hz), 7.7-7.9 (3H, m)

20 APCI- Mass m/z : 237 ($M^+ + 1$).

Preparation 16(2)

To a solution of 2-methoxycarbonyl-5-(4-fluorophenyl)thiophene (1.15 g) in methanol (10 ml) and tetrahydrofuran (10 ml) was added an
25 aqueous solution of sodium hydroxide (1N, 7.3 ml) followed by stirring at 60°C for 3 hours. To the mixture was added hydrochloric acid (1N, 8 ml). The resulting precipitate was collected by filtration and dried to give 5-(4-fluorophenyl)thiophene-2-carboxylic acid (1.06 g, 98.1 %).

NMR (DMSO- d_6 , δ): 7.30 (2H, t, J = 8.8Hz), 7.55 (1H, d, J = 4.4Hz), 7.7-
30 7.9 (3H, m)

ESI- Mass m/z : 223 ($M^+ + 1$).

Example 16

To a suspension of 5-(4-fluorophenyl)thiophene-2-carboxylic acid

(156 mg) and 3-(1,2-dimethylimidazol-5-yl)aniline (131 mg) in dichloromethane (5 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (201 mg) and 4-dimethylaminopyridine (43 mg). The mixture was stirred at ambient temperature for 72 hours and diluted with dichloromethane. The solution was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by a column chromatography (silica gel 25g, 3% methanol in dichloromethane) to give 5-(4-fluorophenyl)thiophene-2-carboxylic acid [3-(2,3-dimethyl-3H-imidazol-4-yl)-phenyl]-amide (240 mg, 88.9 %). NMR (DMSO- d_6 , δ): 2.36(3H, s), 3.56 (3H, s), 6.88 (1H, s), 7.17 (1H, d, J = 7.8 Hz), 7.31 (2H, t, J = 8.9Hz), 7.44 (1H, t, J = 7.9Hz), 7.61 (1H, d, J = 4.0Hz), 7.72 (1H, d, J = 8.0Hz), 8.03 (1H, d, J = 4.0Hz), 10.33 (1H, s) APCI- Mass m/z : 392 ($M^+ + 1$).

Example 17

To a suspension of 2,3-dimethylindole-7-carboxylic acid (95 mg) and 1-hydroxybenzotriazole (81 mg) in dichloromethane (3 ml) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (144 mg), and the mixture was stirred for 5 minutes. After adding 3-(pyrimidin-5-yl)aniline (94 mg) and 4-dimethylaminopyridine (92 mg), the mixture was stirred for 24 hours. The mixture was diluted with dichloromethane and washed with water and brine. The organic layer was dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by a column chromatography (silica gel 25g, 3% methanol in dichloromethane) to give 2,3-dimethyl-1H-indole-7-carboxylic acid (3-pyrimidin-5-yl-phenyl)-amide (117 mg, 68.4 %). NMR (DMSO- d_6 , δ): 2.19 (3H, s), 2.37 (3H, s), 7.10 (1H, t, J = 7.6Hz), 7.5-7.7 (2H, m), 7.63 (1H, d, J = 7.7Hz), 7.77 (1H, d, J = 7.7Hz), 7.9-8.0 (1H, m), 8.30 (1H, s), 9.13 (2H, s), 9.23 (1H, s), 10.38 (1H, s), 10.81 (1H, s) APCI- Mass m/z : 343 ($M^+ + 1$).

Example 18

To a suspension of 9H-carbazole-1-carboxylic acid (112 mg) and

3-(1,3,4-triazol-1-yl)aniline (147 mg) in dichloromethane (3 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (188 mg) and 4-dimethylaminopyridine (43 mg). The mixture was stirred at ambient temperature for 24 hours and diluted with dichloromethane.

5 The solution was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was triturated with methanol. The resulting precipitate was collected by filtration and dried to give 9H-carbazole-1-carboxylic acid (3-[1,2,4]triazol-4-yl-phenyl)-amide (38 mg, 15.4 %).

10 NMR (DMSO- d_6 , δ): 7.20 (1H, t, J = 7.4 Hz), 7.33 (1H, t, J = 7.7 Hz), 7.3-7.5 (2H, m), 7.60 (1H, t, J = 8.0 Hz), 7.72 (1H, d, J = 8.0 Hz), 7.89 (1H, d, J = 8.4 Hz), 8.1-8.3 (3H, m), 8.40 (1H, d, J = 7.5 Hz), 9.09 (2H, s), 10.65 (1H, s), 11.54 (1H, s)
APCI- Mass m/z : 354 ($M^{+}+1$).

15

Example 19

To a suspension of 2-trifluoromethyl-3-methylindole-7-carboxylic acid (122 mg) and 4-methyl-3-(pyrimidin-5-yl)aniline (93 mg) in dichloromethane (5 ml) were added 1-ethyl-3-(3-

20 dimethylaminopropyl)carbodiimide hydrochloride (144 mg) and 4-dimethylaminopyridine (30 mg). The mixture was stirred at ambient temperature for 24 hours and diluted with dichloromethane. The solution was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by a
25 column chromatography (silica gel 25g, 2% methanol in dichloromethane) to give 3-methyl-2-trifluoromethyl-1H-indole-7-carboxylic acid [4-methyl-3-(pyrimidin-5-yl)-phenyl]-amide (155 mg, 75.6 %).

30 NMR (DMSO- d_6 , δ): 2.28 (3H, s), 2.44 (3H, d, J = 2.0 Hz), 7.29 (1H, t, J = 7.7 Hz), 7.3-7.4 (1H, m), 7.8-8.0 (4H, m), 8.90 (2H, s), 9.24 (1H, s), 10.49 (1H, s), 11.44 (1H, s)
APCI- Mass m/z : 411 ($M^{+}+1$).

Example 20

To a suspension of 2-trifluoromethyl-3-methylindole-7-carboxylic acid (122 mg) and 3-(1,2,4-triazol-1-yl)aniline (80 mg) in dichloromethane (5 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (144 mg) and 4-dimethylaminopyridine (30 mg). The mixture was stirred at ambient temperature for 72 hours and diluted with dichloromethane. The solution was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was triturated with methanol. The resulting precipitate was collected by filtration and dried to give 3-methyl-2-trifluoromethyl-1H-indole-7-carboxylic acid [3-(1,2,4-triazol-1-yl)-phenyl]-amide (97 mg, 50.3 %).

NMR (DMSO- d_6 , δ): 2.45 (3H, d, J = 2.0Hz), 7.31 (1H, t, J = 7.7Hz), 7.5-7.7 (2H, m), 7.82 (2H, m), 8.27 (2H, s), 8.51 (1H, s), 9.29 (1H, s), 10.68 (1H, s), 11.53 (1H, s)

APCI- Mass m/z : 386 ($M^+ + 1$).

Preparation 21(1)

A suspension of 5-bromopyrimidine (1.52 g), 2-methylphenylboronic acid (1.43 g), sodium carbonate (3.04 g) and 10 % palladium on charcoal (50 % wet, 0.85 g) was refluxed for 24 hours. The mixture was filtered and the filtrate was concentrated under reduced pressure. To the residue ethyl acetate was added and the mixture was washed with water and brine. The separated organic layer was dried over magnesium sulfate and evaporated under pressure to give 5-(2-methylphenyl)pyrimidine (1.61 g, 98.7 %).

NMR (DMSO- d_6 , δ): 2.27 (3H, s), 7.3-7.5 (4H, m), 8.87 (2H, s), 9.21 (1H, s)

APCI- Mass m/z : 171 ($M^+ + 1$).

Preparation 21(2)

To a suspension of 5-(2-methylphenyl)pyrimidine (0.85 g) in concentrated sulfuric acid (10 ml) was portionwise added potassium nitrate (556 mg) at 5°C. The mixture was stirred at 5°C for 30 minutes and poured into crushed ice. The pH of the mixture was adjusted to 8.0 with an aqueous sodium hydroxide solution (4N) and extracted with ethyl

acetate. The organic layer was washed with water twice and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was triturated with methanol. The resulting precipitate was collected by filtration, washed with methanol and dried to give 5-(2-methyl-5-nitrophenyl)pyrimidine (662 mg, 61.3 %).

NMR (DMSO- d_6 , δ): 2.38 (3H, s), 7.68 (1H, d, $J=8.2$ Hz), 8.2-8.4 (2H, m), 8.96 (2H, s), 9.28 (1H, s)

APCI- Mass m/z : 216 (M^{++1}).

10 Preparation 21(3)

A suspension of 5-(2-methyl-5-nitrophenyl)pyrimidine (0.431 g) in tetrahydrofuran (4 ml) and methanol (4 ml) was hydrogenated over palladium on carbon (10 % w/w, 50 % wet, 129 mg) under hydrogen for 2 hours. The catalyst was filtered off, and the filtrate was evaporated under reduced pressure to give 5-(5-amino-2-methylphenyl)pyrimidine (370 mg, 99.7 %).

NMR (DMSO- d_6 , δ): 2.07 (3H, s), 5.05 (2H, s), 6.48 (1H, d, $J=2.4$ Hz), 6.58 (1H, dd, $J=8.0$ Hz, 2.4 Hz), 6.99 (1H, d, $J=8.0$ Hz), 8.78 (2H, s), 9.16 (1H, s)

20 APCI- Mass m/z : 186 (M^{++1}).

Example 21

To a suspension of 4-methyl-3-(pyrimidin-5-yl)aniline (0.111g) and pyridine (0.15ml) in dichloromethane (2ml) was dropwise added a solution of the fluorene-1-carbonyl chloride (0.137g) in dichloromethane (2 ml) followed by stirring for 2 hours. The mixture was diluted with dichloromethane and washed with an aqueous solution of sodium hydrogen carbonate and brine. The separated organic layer was dried over sodium sulfate and evaporated under reduced pressure. The residue was triturated with methanol. The resulting solid was collected by filtration to give 9H-fluorene-1-carboxylic acid (4-methyl-3-pyrimidin-5-yl-phenyl)-amide (0.167 g, 73.9 %).

NMR (DMSO- d_6 , δ): 2.25 (3H, s), 4.20 (2H, s), 7.3-7.5 (2H, m), 7.5-7.7 (2H, m), 7.7-7.9 (2H, m), 7.97 (1H, d, $J=6.5$ Hz), 8.11 (1H, d, $J=7.1$ Hz), 8.90

(2H, s), 9.24 (1H, s), 10.41 (1H, s)

APCI- Mass m/z : 378 ($M^{++}1$).

Example 22

5 To a suspension of 9H-carbazole-1-carboxylic acid (148 mg) and 1-hydroxybenzotriazole (130 mg) in dichloromethane (3 ml) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (201 mg) and the mixture was stirred for 5 minutes. After adding 4-methyl-3-(pyrimidin-5-yl)aniline (130 mg) and 4-dimethylaminopyridine (128 mg),
10 the mixture was stirred for 24 hours. The mixture was diluted with dichloromethane and washed with water and brine. The organic layer was dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by a column chromatography (silica gel 25g, 2% methanol in dichloromethane) to give 9H-carbazole-1-
15 carboxylic acid (4-methyl-3-pyrimidin-5-yl-phenyl)-amide (140 mg, 52.8 %).

NMR ($DMSO-d_6$, δ): 2.28 (3H,s), 7.20 (1H, t, $J=7.4$ Hz), 7.31 (1H, t, $J=7.8$ Hz), 7.3-7.5 (2H, m), 7.70 (1H, d, $J=8.0$ Hz), 7.86 (1H, d, $J=8.2$ Hz), 7.95 (1H, d, $J=2.0$ Hz), 8.15 (2H, t, $J=7.4$ Hz), 8.37 (1H, d, $J=7.6$ Hz),
20 8.93 (2H, s), 9.25 (1H, s), 10.47 (1H, s), 11.52 (1H, s)
APCI- Mass m/z : 379 ($M^{++}1$).

Preparation 23

To a suspension of 2,2'-bithiophene (1.0 g) in tetrahydrofuran (10
25 ml) was added a solution of n-butyl lithium in n-hexane (1.54 M, 4.3 ml) at -25 °C under nitrogen. The mixture was stirred at -60°C for 30 minutes. To the solution dry-ice (1.0 g) was added and the mixture was stirred at ambient temperature for 30 minutes. To the resultant suspension hydrochloric acid (1N, 10 ml) and ethyl acetate were added.
30 The separated organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was triturated with diisopropyl ether. The resulting precipitate was collected by filtration, washed with diisopropyl ether and dried to give [2,2']bithiophenyl-5-carboxylic acid (952 mg, 75.6 %).

NMR (DMSO- d_6 , δ): 7.14 (1H, t, J = 4.3Hz), 7.35 (1H, d, J = 3.8Hz), 7.4-7.8 (3H, m), 12.5-13.5 (1H, broad s)

APCI- Mass m/z : 211 ($M^+ + 1$).

5 Example 23

To a suspension of [2,2']bithiophenyl-5-carboxylic acid (105 mg) and 1-hydroxybenzotriazole (81 mg) in dichloromethane (2 ml) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (144 mg) and the mixture was stirred for 15 minutes. After adding 3-(1,2-dimethylimidazol-5-yl)aniline (94 mg) and 4-dimethylaminopyridine (92 mg), the mixture was stirred for 24 hours. The mixture was diluted with dichloromethane and washed with water and brine. The mixture was dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by a column chromatography (silica gel 25g, 3% methanol in dichloromethane) to give [2,2']bithiophenyl-5-carboxylic acid [3-(2,3-dimethyl-3H-imidazol-4-yl)-phenyl]-amide (117 mg, 61.6 %).

15 NMR (DMSO- d_6 , δ): 2.36(3H, s), 3.54 (3H, s), 6.88 (1H, s), 7.1-7.2 (2H, m), 7.4-7.6 (3H, m), 7.62 (1H, dd, J = 5.1Hz, 1.1 Hz), 7.7-7.9 (2H, m), 7.99 (1H, d, J = 4.0Hz), 10.33 (1H, s)

20 APCI- Mass m/z : 380 ($M^+ + 1$).

Example 24

This was prepared in a manner similar to Example 12 to give N-3-(imidazol-1-yl)phenyl-1-phenyl-pyrrole-3-carboxamide.

25 mp: 100-103°C (diisopropyl ether/ethyl acetate)

IR (KBr, ν): 1645 cm^{-1}

NMR (DMSO- d_6 , δ): 6.88 (1H, s), 7.13 (1H, s), 7.30-7.80 (10H, m), 8.04 (1H, s), 8.10-8.20 (2H, m), 9.89 (1H, s).

Mass m/z : 329 ($M^+ + 1$).

30

Example 25

To 2-phenyl-thiazole-4-carboxylic acid (70 mg) in 5 mL benzene was added thionyl chloride(0.075 mL) at room temperature. The mixture was heated under reflux for an hour. The mixture was cooled and

evaporated under reduced pressure. To the mixture added was dichloromethane (10ml) followed by 3-(imidazol-1-yl)aniline (54 mg) and triethylamine (0.1 ml). The mixture was stirred at room temperature for an hour. The mixture was washed with a saturated aqueous sodium bicarbonate solution, dried with sodium sulfate and evaporated. The residue was recrystallized from diisopropyl ether/ethyl acetate to give N-3-(imidazol-1-yl)phenyl-2-phenyl-thiazole-4-carboxamide.

mp: 131-134°C (diisopropyl ether/ethyl acetate)

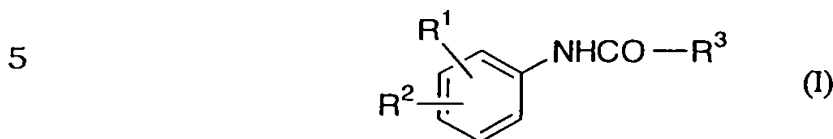
IR (nujol, ν): 1665cm⁻¹

10 NMR (DMSO-d₆, δ): 7.14 (1H, s), 7.42 (1H, d, J=9 Hz), 7.45-7.60 (4H, m), 7.72 (1H, s), 7.94 (1H, d, J=8 Hz), 8.10-8.25 (4H, m), 8.54 (1H, s), 10.41 (1H, s)

Mass m/z : 347 (M⁺+1).

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. An amide compound of the formula (I):



wherein

R¹ is selected from an imidazolyl, triazolyl, pyridyl, pyridazinyl, pyrimidinyl and pyrazinyl group, each of which may be substituted with one or more lower alkyl groups,

R² is a hydrogen atom or a lower alkyl group, and

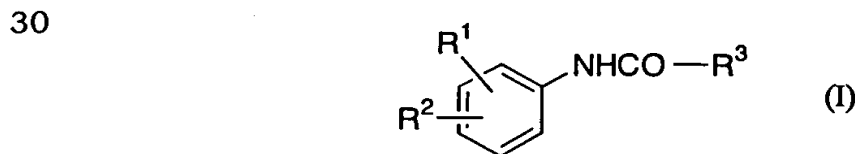
R³ is a phenyl group substituted with thienyl or halophenyl; a thienyl group substituted with thienyl, phenyl or halophenyl; a pyrrolyl group substituted with phenyl; a thiazolyl group substituted with phenyl; an indolyl group substituted with lower alkyl and/or halo(lower)alkyl; a fluorenyl group; or a carbazolyl group, provided that

(1) the imidazolyl group for R¹ is substituted with one or more alkyl groups, when R³ is a phenyl group substituted thienyl; an indolyl group substituted with lower alkyl; or carbazolyl group,

(2) the imidazolyl group for R¹ is substituted with two lower alkyl groups, when R³ is a phenyl group substituted with halophenyl, or

(3) R¹ is pyridyl group, pyridazinyl group, pyrimidinyl group or pyrazinyl group, when R³ is fluorenyl group and its salt.

2. A pharmaceutical composition comprising an amide compound of the formula (I):



wherein

R¹ is selected from an imidazolyl, triazolyl, pyridyl, pyridazinyl, pyrimidinyl and pyrazinyl group, each of which may be substituted with one or more lower alkyl groups,

R² is a hydrogen atom or a lower alkyl group, and

5 R³ is a phenyl group substituted with thienyl or halophenyl; a thienyl group substituted with thienyl, phenyl or halophenyl; a pyrrolyl group substituted with phenyl; a thiazolyl group substituted with phenyl; an indolyl group substituted with lower alkyl and/or halo(lower)alkyl; a fluorenyl group; or a carbazolyl group,

10 provided that

- (1) the imidazolyl group for R¹ is substituted with one or more alkyl groups, when R³ is a phenyl group substituted thienyl; an indolyl group substituted with lower alkyl; or carbazolyl group,
 - (2) the imidazolyl group for R¹ is substituted with two lower alkyl groups, when R³ is a phenyl group substituted with halophenyl, or
 - 15 (3) R¹ is pyridyl group, pyridazinyl group, pyrimidinyl group or pyrazinyl group, when R³ is fluorenyl group
- or its non-toxic pharmaceutically acceptable salt.

Dated this 1st day of October, 1999

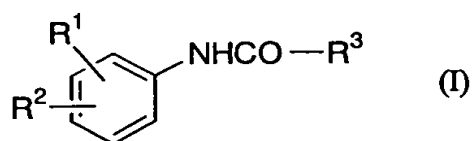
Fujisawa Pharmaceutical Co., Ltd.

By DAVIES COLLISON CAVE
Patent Attorneys for the Applicant

ABSTRACT

Amide compounds of the formula (I):
formula (I):

5



wherein

10 R¹ is selected from an imidazolyl, triazolyl, pyridyl, pyridazinyl, pyrimidinyl and pyrazinyl group, each of which may be substituted with one or more lower alkyl groups,

R² is a hydrogen atom or a lower alkyl group, and

15 R³ is a phenyl group substituted with thienyl or halophenyl; a thienyl group substituted with thienyl, phenyl or halophenyl; a pyrrolyl group substituted with phenyl; a thiazolyl group substituted with phenyl; an indolyl group substituted with lower alkyl and/or halo(lower)alkyl; a fluorenyl group; or a carbazolyl group, and salts thereof which have 5-HT antagonism activity.

20

INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 00/06623

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D403/12 C07D409/12 C07D237/08 C07D239/26 C07D213/40
C07D409/14 A61K31/415 A61K31/41 A61P25/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 23783 A (SMITHKLINE BEECHAM) 8 August 1996 (1996-08-08) page 63 -page 66; claims; tables	1,2
A	US 5 077 409 A (A.WISSNER) 31 December 1991 (1991-12-31) column 21; claims; examples 39-45	1,2
A	US 4 301 169 A (MOTOSUKE YAMANAKA) 17 November 1981 (1981-11-17) the whole document	1,2

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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8 document member of the same patent family

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INTERNATIONAL SEARCH REPORT

information on patent family members

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